

## REMARKS

### **I. Status of the Claims**

1-194 are pending in the application. Claims 133-135 and 137-142 have been examined, as claims 1-132, 136 and 143-194 stand withdrawn pursuant to a restriction requirement and election of species. Claims 140 and 141 are now amended in order to address claim dependency errors resulting from amendments offered in the response filed on May 27, 2003.

### **II. Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 133-135 and 137-142 are again rejected under the first paragraph of §112 as lacking enablement. Applicants traverse the rejection, but in the interest of advancing the prosecution, the claims have been amended to recite subject matter indicated as enabled. Therefore, applicants respectfully request reconsideration and withdrawal of the rejection.

### **III. Rejection Under 35 U.S.C. §103**

#### ***A. Lack of a Prima Facie Case***

Claims 133-135 and 137-142 are again rejected under §103 as obvious over Sobol, Dong, Smith I and Smith II. Sobol is said to teach coadministration of cytokines – not including IFN- $\beta$  - and tumor antigens. Dong is cited as teaching prostate tumor cells expressing IFN- $\beta$  and the reduced metastasis and angiogenesis observed with these cells. Finally, Smith I and II are said to describe adjuvant effects of insect cells, optionally expressing IFN- $\beta$ . From this, the examiner concludes that these references provide sufficient motivation to make and use the claimed invention. Applicants once again traverse.

First and foremost, it is the examiner's burden to establish a *prima facie* case of obviousness. There are three basic criteria that must be satisfied in order for any *prima facie* case to be proper: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. *Manual of Patent Examining Procedure* §2142. See also *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed Cir. 1991). As all three elements must be found to establish a *prima facie* case of obviousness, the absence of but a single element precludes a finding of obviousness.

Applicants previously argued that there was no showing for likelihood of success, and that the rejection was therefore improper on its face. Moreover, as the examiner has acknowledged, "the physiological art is recognized as unpredictable," citing MPEP §2164.03. Office Action, page 6, bottom paragraph. The examiner challenges this line of argument simply by repeating the teachings of the references, and asking the rhetorical question "which specific aspects of the combined teachings are unpredictable?"

Applicants response is that "aspects" of the prior art are not the issue. Rather, the question is whether a scientist could predict, with *reasonable* certainty, that the combination of (a) autologous tumors cells, (b) interferon  $\beta$  and (c) insect cells would have been able to inhibit cancer growth *in a host*. Now, turning to the references, one immediately sees that the Smith references are devoid of *any* teaching with regard to cancer therapy – they simply describe the production of insect cells with various products. Next, Sobol is largely unrelated to the present invention as it relies on *engineered fibroblasts expressing cytokines – none of which are*

*interferon  $\beta$* . Does the examiner suggest that cancer therapy is so predictable that one can ignore the fundamental difference between Sobol and the claimed invention (*ex vivo* treatment of cancer cells using adjuvants and interferon  $\beta$  *versus in vivo* treatment using fibroblast delivery)? Finally, Dong admittedly shows that interferon  $\beta$  has anticancer activity, but it does not indicate that it would have efficacy in an *ex vivo* method in combination with insect cells. Thus, again, it is submitted that the examiner has simply identified various aspects of the claimed invention and, with regard for the inherent unpredictability attendant with cancer therapy, improperly *assumed* that they will work in combination. Simply put, this is not the standard by which obviousness is measured.

Turning next to the motivation prong, applicants have considered the examiner's assertions in this regard, but find them wanting. First, it is quite notable that Sobol, the primary reference, *fails to mention IFN- $\beta$ , while listing numerous other molecules*. This is telling, and in light of the examiner's admission regarding "unpredictability" in the field, it runs counter to scientific principles to simply substitute the teachings of Sobol using IL-2 with IFN- $\beta$ . Moreover, all of Sobol's claims and examples deal with use of *viable* (if non-proliferative) cells that express cytokines upon reintroduction into the host, leading one to the conclusion that the examiner found the use of isolated tumor antigens or inactive cells non-enabled. Thus, applicants submit that the Sobol patent fails to evince, to any degree, that the mere *administration* of IFN- $\beta$  in conjunction with insect cells would be a useful endeavor.

Turning to the Dong reference, applicants certainly see the motivation in combining this article with Sobol, *but again, only to the extent that Sobol discloses viable, non-insect cells that continue to produce IFN- $\beta$* . There would be absolutely no motivation to combine Dong, which teaches the use of transformed prostate cancer cells expressing IFN- $\beta$ , with aspects of Sobol that

include non-viable host cells. Thus, in acknowledging the relationship of Sobol and Dong, applicants submit that they are only related in a way *that has nothing to do with the present invention – viable mammalian cells expressing cytokines*.

Finally, turning to the Smith patents, these references clearly are not combinable with Sobol and Dong for the simple reason that *adjuvants and live cellular cancer vaccines would not be used together*. This is illustrated quite aptly by the fact that (a) Sobol and Dong fail to mention the words “adjuvant” or “insect cells,” and (b) neither of the Smith patents mention transformed non-insect cells, the only common feature between Sobol and Dong. Applicants cannot imagine a better example of how references *fail completely to posit their own combination*, yet it is incumbent upon the examiner to find the suggestion to modify the primary reference *in the prior art*. *In re Soli*, 137 USPQ 797 (CCPA 1963).<sup>1</sup> Thus, for this additional reason, applicants submit that the rejection is improper.

The examiner’s only response to this detailed line of argument is to (a) indicate that the references need not each contain every element of the invention, and (b) that the motivation to modify the prior art may come from the references or knowledge generally available. *This is a statement of law, not evidence of motivation*. The examiner’s restated conclusion at page 12 is simply that – a conclusion. However, just because insect cells *can* express interferon  $\beta$ , and interferon  $\beta$  *can* be used against some cancers, this is not sufficient to show that one of skill in the art would be motivated to *combine* these teachings further with an *ex vivo* cancer therapy using autologous cancer cells. There is simply nothing of record, other than the examiner’s

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<sup>1</sup> “When, as in the instant case, the Patent Office finds, in the words of 35 U.S.C. §103, ‘differences between the subject matter sought to be patented and the prior art,’ it may not, without some basis in logic or scientific principle, merely alleged that such differences are either obvious or of no patentable significance and thereby force an [applicant] to prove conclusively that it is wrong.” *Id.* at 187 USPQ at 801.

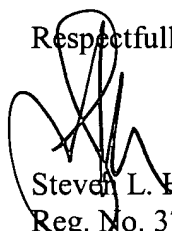
unsupported opinions, that this is so. Again, a proper *prima facie* case of obviousness requires far more than this.

In sum, the examiner has identified references that individually might teach various elements of the claimed invention. However, the rejection is *clearly* based on an impermissible hindsight reconstruction of the invention as the references not only fail to posit their own combination, but actually suggest things other than what is now claimed. *In re Carroll*, 202 USPQ 571 (CCPA 1979) (“One of the more difficult aspects of resolving questions of non-obviousness is the necessity ‘to guard against slipping into the use of hindsight.’”). As such, applicants submit that the rejection is improper; reconsideration and withdrawal is thus respectfully requested.

#### IV. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Should the examiner have any questions regarding this response, a telephone call to the undersigned is invited.

Respectfully submitted,



Steven L. Highlander  
Reg. No. 37,642  
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.  
600 Congress Avenue, Suite 2400  
Austin, Texas 78701  
(512) 474-5201

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